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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/086,177	02/26/2002	Christopher R. Tudan	SMAR-012CIP	1250

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EXAMINER	
BUNNER, BRIDGET E	

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 01/18/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/086,177	TUDAN ET AL.	
	Examiner	Art Unit	
	Bridget E. Bunner	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 October 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-29* is/are pending in the application.

4a) Of the above claim(s) *1-22* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *23-29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-29* are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *26 February 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *11/12/02*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of Application, Amendments and/or Claims

The amendments of 06 August 2002 and 26 October 2004 have been entered in full. Claims 27-29 are added.

Election/Restrictions

Applicant's election with traverse of Group IV, drawn to a CXCR4 agonist peptide and Group J (SEQ IDNO: 13) in the reply filed on 26 October 2004 is acknowledged. The traversal is on the ground(s) that the MPEP permits some discretion on the part of the Examiner to include additional sequences when they have some structural relationship to each other where it makes sense to keep the claims in a single parent. Applicant argues that such is the case here and that there is little additional burden on the Examiner as the sequences are structurally related to each other. Applicant asserts that the CXCR4 agonists of the pending claims have generic linking features of two defined terminal sequences linked through a spacer sequence. Applicant's arguments have been fully considered and are found to be persuasive *in part*. The restriction of the specific SEQ ID NO for the agonist peptide is *withdrawn*. However, the restriction between the inventions of Groups I-IV is maintained for reasons of record (see pages 2-4 of the restriction requirement of 20 September 2004).

Claims 1-22 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 26 October 2004.

Claims 23-29 are under consideration in the instant application.

Inventorship

The submission of the petition under 37 C.F.R. § 1.47(a) on 06 August 2002 to file the instant application by inventors Merzouk, Lakhdar, Saxena, Eaves, Cashman, Clark-Lewis, and Salari on behalf of Tudan is granted. It is noted that Tudan may subsequently join in the application by filing an oath or declaration complying with 37 C.F.R. § 1.63.

Specification

1. The disclosure is objected to because of the following informalities:

2. At pg 60, the specification refers to Table 4. The table shown on pg 60 is labeled as Table 3. However, a Table 4 is first disclosed on page 55 of the specification. Therefore, the Table at pg 60 should be labeled "Table 5". Additionally, lines 6, 9, and 16 on pg 60 should be amended to refer to "Table 5" rather than "Table 4".

3. Claim 28 is objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim cannot depend from any other multiple dependent claim. See MPEP § 608.01(n).

4. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed.

The following title is suggested: "CXC CHEMOKINE RECEPTOR 4 AGONIST PEPTIDE".

Appropriate correction is required.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it

pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 23-28 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a CXC chemokine receptor 4 (CXCR4) agonist peptide comprising (a) an N-terminal sequence comprising amino acids 1-14 of stromal cell derived factor-1 (SDF-1); (b) a C-terminal sequence comprising amino acid 55-67 of SDF-1 and wherein the C-termini is an acid or an amide; (c) a peptide spacer sequence linking the N-terminal sequence to the C-terminal sequence, wherein the peptide spacer sequence comprises 4 glycine residues; and optionally (d) an internal cyclic lactam bond between amino acid residues 20 and 24 in the C-terminal sequence of the peptide agonist wherein residue 24 is E or D, does not reasonably provide enablement for a CXCR4 agonist peptide comprising (a) a N-terminal sequence homologous to an SDF-1 N-terminal sequence; (b) a C-terminal sequence homologous to an SDF-1 C-terminal sequence; and (c) a peptide spacer sequence linking the N-terminal sequence to the C-terminal sequence. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Specifically, the claims are directed to a CXCR4 agonist peptide comprising (a) a N-terminal sequence homologous to an SDF-1 N-terminal sequence; (b) a C-terminal sequence homologous to an SDF-1 C-terminal sequence; and (c) a peptide spacer sequence linking the N-terminal sequence to the C-terminal sequence. The claims also recite that the agonist further comprises an internal cyclic amide bridge formed between a carboxylic acid side chain on a first amino acid residue and an amide side chain on a second amino acid residue. The claims recite that the agonist comprises an internal cyclic disulphide or lactam bond and that the internal

cyclic amide bridge is in the C-terminal sequence. The claims recite that the peptide is selected from the group consisting of polypeptides having the sequence of SEQ ID NO: 12 to 27.

The specification of the instant application teaches that SDF-1(1-14)-$(G)_4$-SDF-1(55-67)-amide (also referred to as CTCE0017; SEQ ID NO: 15) inhibits cell cycling in human positive erythroid and primitive granulocyte cells (pg 52, lines 1-5; Table 2). The specification discloses that SDF-1(1-14)-$(G)_4$-SDF-1(55-67)-K20/D24-cyclic amide (SEQ ID NO: 25) inhibits the cyclic activation of BFU-E and CFU-GM progenitor stem cells in the adherent layer of LTC (pg 56, lines 17-22; Figure 6). The specification teaches that SDF-1(1-14)-$(G)_4$-SDF-1(55-67)-acid (also referred to as CTCE0013; SEQ ID NO: 13) represses the proliferation of clonogenic erythroid and granulopoietic progenitors in an *in vitro* LTC-IC assay (pg 55, lines 1-21; Table 4; Figures 7). Finally, the specification teaches that SDF-1(1-14)-$(G)_4$-SDF-1(55-67)-K20/E24-cyclic amide (also referred to as CTCE0021; SEQ ID NO: 23) inhibits cell cycling in human positive erythroid and primitive granulocyte cells (pg 52, lines 1-5; Table 2), represses the proliferation of clonogenic erythroid and granulopoietic progenitors in an *in vitro* LTC-IC assay (pg 55, lines 1-21; Table 4; Figure 7), significantly ameliorates the decrease in white blood cell count caused by Ara-C (pg 52, lines 20-25; Figure 1), inhibits the cytotoxic effects of Ara-C, and sustains a higher level of leukocytes *in vivo* as compared to control (pg 59, lines 1-7; Figures 10-11). However, the specification does not teach all possible CXCR4 agonist peptides comprising (a) a N-terminal sequence homologous to an SDF-1 N-terminal sequence; (b) a C-terminal sequence homologous to an SDF-1 C-terminal sequence; and (c) a peptide spacer sequence linking the N-terminal sequence to the C-terminal sequence. Undue experimentation would be required of one skilled in the art to generate the infinite number of CXCR4 peptides recited in

the claims and screen the same for activity. Applicant's broad brush discussion of making and screening for CXCR4 agonists at pg 22, lines 12-32 and pg 27, 29-30 of the specification constitutes an invitation to experiment by trial and error. This is not adequate guidance, but is merely an invitation to the artisan to use the current invention as a starting point for further experimentation. For example, other than amino acids 1-14 of the N-terminal sequence of SDF-1 and amino acids 55-67 of the C-terminal sequence of SDF-1, there is little guidance in the specification indicating which amino acids from the N-terminal domain and which amino acids from the C-terminal domain of SDF-1 can be linked to together to generate a functional agonist peptide. Additionally, the skilled artisan must resort to trial and error experimentation to determine which compounds might yield one with the desired agonistic activity. Such trial and error experimentation is considered undue.

Due to the large quantity of experimentation necessary to identify and screen all possible CXCR4 agonists, the lack of direction/guidance presented in the specification regarding the same, the absence of working examples directed to the same, the complex nature of the invention, and the breadth of the claims which fail to recite any specific peptide structural limitations, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

7. Claims 23-27 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant

art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are directed to a CXCR4 agonist peptide comprising (a) a N-terminal sequence homologous to an SDF-1 N-terminal sequence; (b) a C-terminal sequence homologous to an SDF-1 C-terminal sequence; and (c) a peptide spacer sequence linking the N-terminal sequence to the C-terminal sequence. The claims also recite that the agonist further comprises an internal cyclic amide bridge formed between a carboxylic acid side chain on a first amino acid residue and an amide side chain on a second amino acid residue. The claims recite that the agonist comprises an internal cyclic disulphide or lactam bond and that the internal cyclic amide bridge is in the C-terminal sequence. The claims recite that the peptide is selected from the group consisting of polypeptides having the sequence of SEQ ID NO: 12 to 27.

As mentioned above, the specification of the instant application teaches that SDF-1(1-14)-$(G)_4$-SDF-1(55-67)-amide (also referred to as CTCE0017; SEQ ID NO: 15) inhibits cell cycling in human positive erythroid and primitive granulocyte cells (pg 52, lines 1-5; Table 2). The specification discloses that SDF-1(1-14)-$(G)_4$-SDF-1(55-67)-K20/D24-cyclic amide (SEQ ID NO: 25) inhibits the cyclic activation of BFU-E and CFU-GM progenitor stem cells in the adherent layer of LTC (pg 56, lines 17-22; Figure 6). The specification teaches that SDF-1(1-14)-$(G)_4$-SDF-1(55-67)-acid (also referred to as CTCE0013; SEQ ID NO: 13) represses the proliferation of clonogenic erythroid and granulopoietic progenitors in an *in vitro* LTC-IC assay (pg 55, lines 1-21; Table 4; Figures 7). Finally, the specification teaches that SDF-1(1-14)-$(G)_4$-SDF-1(55-67)-K20/E24-cyclic amide (also referred to as CTCE0021; SEQ ID NO: 23) inhibits cell cycling in human positive erythroid and primitive granulocyte cells (pg 52, lines 1-5; Table

2), represses the proliferation of clonogenic erythroid and granulopoietic progenitors in an *in vitro* LTC-IC assay (pg 55, lines 1-21; Table 4; Figure 7), significantly ameliorates the decrease in white blood cell count caused by Ara-C (pg 52, lines 20-25; Figure 1), inhibits the cytotoxic effects of Ara-C, and sustains a higher level of leukocytes *in vivo* as compared to control (pg 59, lines 1-7; Figures 10-11). However, to provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of compete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. In this case, the only factor present in the claims is a partial structure in the form of broad N-terminal, C-terminal, and linker recitations. There is not even identification of any particular portion of the structure or sequence of SDF-1 that must be conserved. Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed"* (See page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed" (See *Vas-Cath* at page 1116).

The skilled artisan cannot envision the detailed chemical structure of the encompassed CXCR4 agonist polypeptides, and therefore conception is not achieved until reduction to practice

has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The nucleic acid itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, only an isolated CXCR4 agonist peptide comprising (a) an N-terminal sequence comprising amino acids 1-14 of stromal cell derived factor-1 (SDF-1); (b) a C-terminal sequence comprising amino acid 55-67 of SDF-1 and wherein the C-termini is an acid or an amide; (c) a peptide spacer sequence linking the N-terminal sequence to the C-terminal sequence, wherein the peptide spacer sequence comprises 4 glycine residues; and optionally (d) an internal cyclic lactam bond between amino acid residues 20 and 24 in the C-terminal sequence of the peptide agonist wherein residue 24 is E or D, but not the full breadth of the claim meets the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

35 USC § 112, second paragraph

8. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claims 23-29 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

10. Claim 28 is indefinite because the SEQ ID NOs recited in the claim do not constitute proper Markush groups. See MPEP § 2173.05(h).

11. Regarding claims 23-29, the acronyms "CXCR4" and "SDF-1" render the claims vague and indefinite. Abbreviations should be spelled out in all independent claims for clarity.

Claim Rejections - 35 USC § 102

12. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

13. Claims 23 and 25 are rejected under 35 U.S.C. 102(a) as being anticipated by Luo et al (Biochem Biophys Res Comm 264: 42-47, 1999).

Luo et al. teach an agonist peptide comprising (a) an N-terminal sequence of SDF-1 (amino acids 5-14), (b) a C-terminal sequence of SDF-1 (amino acids 55-67), and a peptide spacer sequence comprising 4 glycine residues (Figure 1; pg 46, col 2). Luo et al. also disclose that the peptide comprises an internal cyclic disulphide bond between 2 amino acids (pg 43, 2nd full paragraph). (It is noted that in the experimental procedures section (pg 43, 2nd full paragraph), Luo et al. indicate that the peptides are generated by using previously described methods which disclose the creation of cyclized disulfide peptides. One of the cited references

(Li et al., J Biol Chem 273(26): 16442-16445, 1998) teach that cyclization of disulfide peptides is achieved (pg 16444, col 1).)

Conclusion

No claims are allowable.

The art made of record and not relied upon is considered pertinent to applicant's disclosure:

Tudan et al. Med Chem. 45(10):2024-2031, 2002. (C-terminal cyclization of SDF-1 peptide analog)

Loetscher et a. J Biol Chem 273(35) : 22279-22283, 1998. (N-terminal peptides of SDF-1 have agonist and antagonist activities)

Perez et al. Exp Hematol 32 : 300-307, 2004 (SDF-1 peptide agonist (CTCE0214) mobilized human colony-forming cells and enhanced thrombopoiesis)

Zhong et al. Exp Hematol 32 : 470-475, 2004. (SDF-1 peptide analogs enhance chemotaxis of normal and G-CSF mobilized hematopoietic cells)

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bridget E. Bunner whose telephone number is (571) 272-0881. The examiner can normally be reached on 8:30-4:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda Brumback can be reached on (571) 272-0961. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

BEB
Art Unit 1647
12 January 2005

Bridget E. Bunner